

Pharmaceutical 3-A[®] Sanitary/Hygienic Standards for Materials for Use in Process Equipment and Systems

P3-A 002

*Formulated by
3-A Sanitary Standards, Inc.
Pharmaceutical 3-A (P3-A) Steering Committee*

It is the purpose of the Pharmaceutical 3-A (P3-A) Steering Committee in connection with the development of the Pharmaceutical 3-A Sanitary/Hygienic Standards Program to allow and encourage full freedom for inventive genius or new developments. Materials for Use in the Pharmaceutical Process Environment in equipment and systems heretofore or hereafter developed which so differ in design, materials, and fabrication or otherwise as not to conform to the following standards but which, in the manufacturer's opinion, are equivalent or better, may be submitted for the joint consideration of the Pharmaceutical 3-A Steering Committee and 3-A Sanitary Standards, Inc. at any time. The Pharmaceutical 3-A (P3-A) Sanitary/Hygienic Standards and Pharmaceutical 3-A Accepted Practices provide hygienic criteria applicable to equipment and systems used to produce, process, and package active pharmaceutical ingredient(s). Standard English is the official language of Pharmaceutical 3-A Sanitary/Hygienic Standards and Pharmaceutical 3-A Accepted Practices.

A SCOPE

- A1 These sanitary/hygienic standards provide minimum materials and surface property requirements, including minimum fabrication related materials and surface property requirements for equipment and components utilized in the pharmaceutical manufacturing environment whereby those material and surface properties may directly, indirectly, or incidentally impact the strength, identity, safety, purity or quality of the active pharmaceutical ingredient, excipient, or drug product.
- A2 Subject materials include metals, non-metals (i.e. polymerics, plastics, elastomers, ceramics, glass, lubricants, sealants, and adhesives), and their processed forms intended for single or multiple-use as direct, indirect, or incidental product contact and/or cleaning solution (aqueous and/or non-aqueous) contact surfaces in equipment for production, processing, and handling of the active pharmaceutical ingredient, excipient, or drug product.
- A3 This standard shall apply to new equipment.
- A4 See Appendix A for those manufacturing steps for which this standard intended to apply.

B NORMATIVE REFERENCES

- 21 CFR 210 cGMP Practice in Mfg, Processing, Packaging, or Holding of Drugs.
- 21 CFR 211 cGMP for Finished Pharmaceuticals.
- 21 CFR 175 Indirect Food Additives: Adhesives and Components of Coatings.
- 21 CFR 176 Indirect Food Additives: Paper and Paperboard Components.
- 21 CFR 177 Indirect Food Additives: Polymers.
- 21 CFR 178 Indirect Food Additives: Adjuvants, Production Aids, and Sanitizers.
- 21 CFR 820 Quality System Regulation.
- ISO 2743 Vitreous and porcelain enamels - Determination of resistance to condensing hydrochloric acid vapor.
- ISO 13807 Vitreous and porcelain enamels - Determination of crack formation temperature in the thermal shock testing of enamels for the chemical industry.
- ISO 2723 Vitreous and porcelain enamels for sheet steel - Production of specimens for testing

ISO 2733 Vitreous and porcelain enamels - Apparatus for testing with acid and neutral liquids and their vapors.

ISO 2734 Vitreous and porcelain enamels - Apparatus for testing with alkaline liquids.

ISO 2745 Vitreous and porcelain enamels - Determination of resistance to hot sodium hydroxide.

ISO 3601-1 Fluid power systems - O-rings - Part 1: Inside diameters, cross-sections, tolerances and size identification code.

ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients.

ICH Q1A Stability Testing of New Drug Substances and Products.

United States Pharmacopoeia (current Edition).

ASTM A380 Standard Practice for Cleaning, Descaling, and Passivation of Stainless Steel Parts, Equipment, and Systems.

ASTM D395 Compression Set – Rubber.

ASTM B912 Standard Specification for Passivation of Stainless Steels Using Electropolishing.

ASTM D2240 Rubber Property – Durometer Hardness.

ASTM G31 – Laboratory Immersion Corrosion Testing of Metals.

ASME B46.1 – Surface Texture.

AWS D18.1 Specification for Welding of Austenitic Stainless Steel Tube and Pipe Systems in Sanitary (Hygienic) Applications.

Steel Products Manual: Stainless Steels – Iron & Steel Society – ISBN: 1-886362-34-3.

NSF White Book™ - Lubricant Reference.

P3-A – 001 General Glossary of Terminology Used In Pharmaceutical 3-A® Standards.

Machinery's Handbook, 27th Edition, Industrial Press Inc., New York, NY

B1 Acronyms

AISI: American Iron and Steel Institute
 ANSI: American National Standards Institute
 API: Active Pharmaceutical Ingredient
 ASME: American Society of Mechanical Engineers
 ASTM: American Society for Testing and Materials
 AWS: American Welding Society
 BCC: Body centered cubic
 CFR: Code of Federal Regulations
 CFU: Colony forming units
 CIP: Clean-In-Place
 COP: Clean out of place
 FCC: Face centered cubic
 GRAS: Generally Recognized As Safe
 HAZ: Heat affected zone
 HDPE: High density polyethylene
 ICH: International Conference on Harmonization
 NDA: New Drug Application
 PFA: Perfluoroalkoxy
 PE: Polyethylene
 P: Polypropylene.
 PTFE: Polytetrafluoroethylene
 PVDF: Polyvinylidene fluoride
 QA: Quality assurance
 QC: Quality control
 SAE: Society of Automotive Engineers
 UNS: Unified Numbering System
 USP: United States Pharmacopoeia

B2 Definitions

Terminology and definitions used in this standard and other Pharmaceutical 3-A Standards are provided in the document *General Glossary of Terminology Used in Pharmaceutical 3-A® Standards, P3-A 001*.

C MATERIALS

All product contact materials of construction shall be capable of service in the environment of intended use without significantly degrading product specifications regarding product safety, identity, quality, and purity. Particular attention shall be paid to selection of materials that will retain requisite surface characteristics and chemistry despite prolonged and-or repeated exposure to product, cleaning, and maintenance over the anticipated life of the system in which they are used. Such selection shall be based upon credible testing and-or extended operating experience where the subject characteristics were in fact observed and recorded.

The requirements of the pharmaceutical environment are sufficiently varied that a material or surface finish suitable for one application may be unsuitable for another. The materials listed here constitute a baseline from which to begin the material selection process. Definitive acceptance is

not implied for specific applications except for some instances of water.

The specific P3-A Equipment Standard shall define the minimum surface finish and performance characteristics of any material(s) selected for use in fabrication of the equipment.

Equipment will wear and undergo changes from like-new condition. Selection of materials, finishes, and fabrication methods shall be based upon understanding of the environment of intended use. The owner/user shall accordingly be responsible for the final selection of materials of construction and surface finishes and associated rationales with regard to product safety, identity, quality, and purity.

C1 Metallic Materials

Metallic materials used as product contact and/or cleaning solution contact surfaces shall be resistant to corrosive attack that would adversely affect the system performance. The acceptable corrosion rate shall be defined by the process requirements. In no case shall the general corrosion rate exceed 0.010 inches (0.254mm) per year. These materials shall be nontoxic and non-absorbent to the extent required by ICH Q7A. Alloys containing lead, leachable copper, or other toxic metals are not to be used.

Refer to Appendix B, Metals Tables, for composition data for alloys that have application in the fabrication of equipment having product contact surfaces. The application of any metal alloy shall demonstrate a corrosion resistance of at least that of 300 Series Stainless Steel as shown when tested in accordance with ASTM G31 – Laboratory Immersion Corrosion Testing of Metals. Refer to Appendix C for a discussion of corrosion.

C1.1 Application environments requiring high strength, high wear resistance, high chemical resistance, or other qualities may require selections of metallic materials that are application specific.

(Example: The storage of butyl lithium in a carbon steel vessel is an acceptable method that does not require use of a high alloy or exotic material.)

C1.2 Metallic Welding

Filler metals used in welding procedures shall be capable of producing welds at least as strong and as corrosion resistant as the parent metal.

See Appendix D for Recommended Guidelines for Welding Metals.

C1.3 Metallic Surface Treatments

Metallic surface treatments are processes where chemical compositions or mechanical properties of the existing surface are altered.

Surface treatments include:

- Thermal (surface hardening laser, electron beam)
- Diffusion (carburizing, nitriding)
- Chemical (etching, oxidation, passivation)
- Ion Implantation
- Mechanical (grinding, polishing, shot peening)
- Electropolishing

For more information on surface treatments, see Machinery's Handbook.

C2 Coatings

C2.1 Coatings, Overlays and Encapsulations:

C2.1.1 Coatings, overlays and encapsulations may be a metallic or non-metallic layer of material covering a substrate. The layer does not alter the physical properties of the substrate.

Coating processes include:

- Chemical (conversion coatings except anodizing)
- Engineering Plating (e.g. gold plating, Thin Dense Chrome (TDC))
- Electroless Deposition
- Thermal spraying (e.g., flame, plasma, or arc spray, of metallic or non-metallic material)
- Physical Vapor Deposition
- Chemical Vapor Deposition

C2.2 Coatings, when used, shall be free from delamination, pitting, flaking, spalling, blistering, or distortion when exposed to the conditions encountered in the environment of intended use including cleaning and sanitizing treatment or sterilization.

C2.2.1 Electrodeposited coatings shall be at least 0.0002 in. (0.005 mm) thick.

C2.2.2 Thermospray materials coatings shall be at least 0.003 in. (0.08 mm) thick.

C2.2.3 Plastic or rubber and rubber-like materials, when used as a coating, overlay, or encapsulation, shall be at least 0.001 in. (0.025 mm) thick.

C3 Bonded Materials

Plastic or Synthetic Elastomer materials may be bonded. The bond shall be continuous and mechanically sound. The plastic or synthetic elastomer material shall not separate from the base material to which it is bonded when exposed to the conditions encountered in the environment of intended use and in cleaning and sanitizing treatment or sterilization.

C4 Plastic Materials and Synthetic Elastomers

Plastic materials and synthetic elastomers used as product contact and/or cleaning solution contact surfaces shall be nontoxic and shall comply with FDA regulations of the Food, Drug and Cosmetic Act. Plastic materials complying with The Code of Federal Regulations, Title 21, Part 177 (21CFR177) shall be selected to be relatively unaffected when subjected to normal cleaning and bactericidal treatment. Only virgin, unadulterated or clean in-process and/or properly stored re-grind plastic materials shall be used. Plasticizers, and plastic additives, if used, shall be used at the minimum levels required for the desired functionality and also be used in accordance with the conditions prescribed by current federal regulations or the FD&C Act as amended.

See Table 1 for the Plastics and Synthetic Elastomers included in these standards.

- C4.1 Plastic and synthetic elastomer materials providing starter, intermediate, final API, and excipient product contact surfaces and/or cleaning solution contact surfaces that are encountered prior to the final API isolation and purification process shall be certified to comply with 21CFR177.
- C4.2 Plastic and synthetic elastomer materials providing topical and oral dose product contact surfaces and/or cleaning solution contact surfaces that are encountered during or after the final API isolation and purification process shall be certified to comply with 21CFR177.
- C4.3 Plastic and synthetic elastomer materials providing injectable and breach contact product contact surfaces and/or cleaning solution contact surfaces that are encountered during or after the final API purification process shall be certified to comply with United States Pharmacopoeia Class IV, V, or VI as applicable.

- C.4.4 Certification of each formulation for compliance with FDA regulations and/or FD&C Act requirements and compliance with the criteria herein are shall be maintained by the manufacturer and supplier. This information shall be made available to distributors, users, and regulatory agencies upon request. See Appendix F for an example of the Plastic or Synthetic Elastomer Material Certification Form.

TABLE 1 – Plastics and Synthetic Elastomers Included in These Standards

Generic Classes	Code of Federal Regulations Citation (CFR references) *
Acrylics	21 CFR 177.1010
Acrylonitrile butadiene styrene	21 CFR 177.1020
Chlorinated polyether	21 CFR 177.2430
Cross-linked polyester resins (vinyl ester-styrene copolymer) (	21 CFR 177.2420)
Epoxy resin as coating (x) (a) Isopropylidenediphenol Hardener-TETA Triethylenetetramine (b) Phenol-Formaldehyde Polymer, glycidyl ether (silica filled) Hardener - DETA Adduct	21 CFR 175.300
Ethylene-vinyl acetate copolymers	21 CFR 177.1350
Fluoropolymers: CTFE, PTFE, FEP, PFA, PVDF and ETFE types;	21 CFR 170.39, 177.1380, 177.1550, 177.2510, 177.2600)
Nylon: Type 6, Type 66, Type 610, Type 11, Type 12	21 CFR 177.1500
Nylon 66-Nylon 6-aramid fiber blend	21 CFR 177.1500, 177.1632
Nylon 66-Nylon 6-aramid fiber-PTFE blend (	21 CFR 177.1500, 177.1380, 177.1632)
Plasticized polyvinyl chloride (a) For contact with high-water, low-fat products (b) For contact with high-fat products (>8% fat)	21 CFR 175.300
Poly (aryletherketone) (PEEK) resins	21 CFR 177.2415
Polyarylsulfone resin	21 CFR 177.1560
Polycarbonates	21 CFR 177.1580
Polyetherimide	21 CFR 177.1595
Polyethylene: ASTM Type I, Type II., ultra-high molecular weight (UHMWPE)	21 CFR 177.1520
Polyethylene phthalate polymers	21 CFR 177.1630
Polymethylpentene	21 CFR 177.1520
Polyoxymethylene copolymer	21 CFR 177.2470
Polyoxymethylene homopolymer	21 CFR 177.2480
Polyphenylene oxide	21 CFR 177.2460
Polyphenylene sulfide	21 CFR 177.2490
Polyphenylene sulfide-PTFE (alloy)	21 CFR 177.2490, 177.1380
Polyphenylsulfone (repeated use)	
Polypropylene - (unmodified and modified for impact resistance)	21 CFR 177.1520
Polystyrene - Normal (unmodified) Type 3 of ASTM D703-78	21 CFR 177.1640
Polystyrene - Modified (impact), Type III, Grade 6, of ASTM D1892-78	21 CFR 177.1640
Polysulfone resin	21 CFR 177.1655
Polysulfone-PTFE (alloy)	21 CFR 177.1655, 177.1380
Polytetramethylene terephthalate	21 CFR 177.1660
Polytetramethylene terephthalate-PTFE blend	21 CFR 177.1660, 177.1380
Polyurethane	21 CFR 177.1680
Propoxylated bisphenol-A fumarate polyester-styrene copolymer	21 CFR 177.2420
Reinforced epoxy, molded, natural (no color added), and black	21 CFR 175.300
Styrene-acrylonitrile	21 CFR 177.1040
Thermoplastic polyether-ester (EPDM)	21 CFR 177.2600

* CFR references include the basic polymers, optional adjuvants, specifications, and limitations and conditions of use.

C4.5 Plastic Welding

Filler materials used in welding procedures shall preserve the corrosion resistance and surface finish of the parent plastics being joined. The resulting welded joint and surrounding parent material shall be at least as strong and as corrosion resistant as the original parent material.

Acceptable plastic welding procedures are described in American National Standard AWS B2.4:2006, Specification for Welding Procedure and Performance Qualification of Thermoplastics.

C5 Ceramic, Glass and Glass-lined Materials

C5.1 For many materials the chemical composition can serve as the basis for specifying the material and determining if the material meets the quality requirements. This is not possible for glass-lined process equipment because the coating composition is tied very closely to the specific coating technique and substrate material chemistry and properties. In order to ascribe measurable attributes to the glass or glass-ceramic lining, besides its general designation, the manufacturer conducts standardized tests and specifies the material in terms of resistance to corrosion and thermal shock. The following values shall represent the minimum requirements of a glass or glass-ceramic lining.

C5.1.1 Corrosion rate in acid (acid resistance) shall be less than 0.0031 inches per year. Sample preparation shall be in accordance with ISO 2723. Test apparatus shall be in accordance with ISO 2733. Test procedures shall be in accordance with ISO 2743.

C5.1.2 Corrosion rate in alkali (alkali resistance) shall be less than 0.0157 inches per year. Sample preparation shall be in accordance with ISO 2723. Test apparatus shall be in accordance with ISO 2734. Test procedures shall be in accordance with ISO 2745.

C5.1.3 Thermal shock resistance vessels shall be a minimum of 342°F. Accessories (agitator, baffle, etc.) shall have a minimum thermal shock resistance of 306°F. Sample preparation, test apparatus and test procedures shall be in accordance with ISO 13807.

C5.1.4 After selection of the desired coating system the owner/user shall, in concert with the manufacturer, specify the required quality details of the glass-lining. Base quality details shall include glass type

and color, glass thickness and voltage test requirements.

C5.1.5 Consideration of cleaning and sanitizing materials and procedures required by the product and process shall also be made by the owner/user to ensure that the process contact surfaces are cleanable and the selected cleaning process does not adversely affect the lining as a suitable material for subsequent product contact.

C6 Solid Ceramic and Glass

Solid Ceramic or Glass materials are considered acceptable for use as materials for product contact applications.

C7 Adhesives and Sealants

C7.1 The use of adhesives and sealants as components of articles intended for use in manufacturing, packaging, transporting, or holding active pharmaceutical ingredients, excipients, or drug products shall comply with 21CFR175 - Indirect Food Additives: Adhesives and Components of Coatings.

The adhesive or sealant shall be prepared from one or more of the optional substances named in paragraph (c) of Section 175.105 subject to any limitations prescribed therein. Further, the adhesive or sealant shall be separated from the product by a functional barrier. Any optional materials used in the formulation of an adhesive or sealant shall be Generally Recognized As Safe (GRAS), except that;

C7.2 Use of PTFE tape as a thread sealant is an approved method where threaded joints are allowed.

C8 Lubricants

Lubricants shall not be chemically reactive with equipment surfaces or product and shall not be used as a direct product contact surface.

C8.1 H1 Lubricants with Incidental Product Contact

C8.1.1 Lubricant utilized where incidental product can occur with starter, intermediate, final API, and excipient product surfaces and/or cleaning solution contact surfaces that are encountered prior to the final API isolation and purification process shall be certified to comply with NSF classification H1 as "Food Grade Lubricant." **The amount used should be the minimum required to accomplish the**

desired technical effect on the equipment.

- C8.1.2 Lubricant utilized where incidental product can occur with topical and oral dose product contact surfaces and/or cleaning solution contact surfaces that are encountered during or after the final API isolation and purification process shall be certified to comply with NSF classification H1 as “Food Grade Lubricant. **The amount used should be the minimum required to accomplish the desired technical effect on the equipment.**
- C8.1.3 Lubricant utilized where incidental product can occur with injectable and breach contact product contact surfaces and/or cleaning solution contact surfaces that are encountered during or after the final API purification process shall be certified to comply with United States Pharmacopoeia Class IV, V, or VI as applicable. **The amount used should be the minimum required to accomplish the desired technical effect on the equipment.**